

# A Bidomain Model for Lens Microcirculation

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## Abstract

There exists a large body of research on the lens of mammalian eye over the past several decades. The objective of the current work is to provide a link between the most recent computational models and some of the pioneering work in the 1970s and 80s. We introduce a general non-electro-neutral model to study the microcirculation in lens of eyes. It describes the steady state relationships among ion fluxes, water flow and electric field inside cells, and in the narrow extracellular spaces between cells in the lens. Using asymptotic analysis, we derive a simplified model based on physiological data and compare our results with those in the literature. We show that our simplified model can be reduced further to the first generation models while our full model is consistent with the most recent computational models. In addition, our simplified model captures the main features of the full model. Our results serve as a useful link intermediate between the computational models and the first generation analytical models. Simplified models of this sort may be particularly helpful as the roles of similar osmotic pumps of microcirculation are examined in other tissues with narrow extracellular spaces, like cardiac and skeletal muscle, liver, kidney, epithelia in general, and the narrow extracellular spaces of the central nervous system, the “brain”. Simplified models may reveal the general functional plan of these systems before full computational models become feasible and specific.

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## 1. Introduction

Biological systems require continual inputs of mass and energy to stay alive. They are open systems that require flow of matter, and specific chemicals, across their boundaries. Unicellular organisms can provide that flow by diffusion to and across cell membranes. Diffusion is not adequate over distances larger than a few cell diameters, i.e., larger than say  $2 \times 10^{-6}$  meters, to pick a number. For that reason, multicellular organisms cannot provide those flows to their cells by diffusion itself. Multicellular organisms depend on

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convection to bring materials close enough to cells so diffusion to and across cell membranes can provide what the cell needs to live.

The circulatory system of blood vessels-arteries, veins, and capillaries-provides the convection in almost all tissues. But there is one clear exception, the lens of the (mammalian) eye. The lens does not have blood vessels, presumably because even capillaries would so seriously interfere with transparency. The lens is large, much larger than the length scale on which diffusion itself is efficient. The lens must provide nutrients through another kind of convection, a microcirculation of water that moves nutrients into the lens and rinses wastes out of it. The microcirculation is in fact driven by the lens itself, without an external 'pump'. The lens is itself an osmotic pump.

The lens is an asymmetrical electrical syncytium in which all cells are electrically coupled one to another, with a narrow extracellular space between the cells (see Fig.1). The extracellular space is filled with ionic solution in free diffusion with the plasma outside cells. It may also contain specialized more or less immobile proteins and specialized polysaccharides, as well as containing obstructions formed by the connexin proteins themselves. The intracellular space behaves very much as a large single cell would, with the bio-ions of classical electro-physiology ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cl}^-$ ) free to move without much resistance from cell to cell, and many solutes of significant size (say with diameter less than 1.5 nm) able to move as well. The intracellular media contains proteins particularly the crystallins responsible for the high refractive index of the lens. So the lens is an example of a bidomain tissue that has been studied in some detail, first in skeletal muscle, then in cardiac muscle, and syncytia in general. Electrical models of bidomain tissues have been developed and a general approach combining morphology, theory, and experiments has been applied in reference [1], showing how the lens could be studied in this tradition.

A general approach to bidomain tissues was implemented [2] involving detailed measurements of morphology (best done with statistical sampling by stereo-logical methods [3]), impedance spectroscopy [4, 5, 6, 7, 8, 9, 10] using intracellular probes (micro-electrodes) that force current to flow across membranes to the extracellular baths [11, 1, 12, 13, 14, 15], electric field theory to develop models appropriate to the structure [16, 17, 18, 19, 20] analyzing the spectroscopic data with the field theory [21, 22] and checking that parameters change appropriately (i.e., estimates of membrane capacitance are constant) as extracellular solutions are changed in composition and concentration [20, 23]. This work was extended to deal with transport by Mathias and co-workers [24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40] and computational models of the water flow in the lens were later developed in some detail [25, 41, 42] and exploited with great success, reviewed in [43, 44], also see [45, 46, 47, 48, 49].

The original work on electrical models is cited here because it provides coherent support, involving a range of techniques and approaches, to the general view of syncytial tissues, used here and in later work. It also shows the range of approaches needed to establish a (then) new view of a tissue.

Mathias [50, 51] realized that an asymmetrical electrical syncytium would produce convection, in particular in the lens [31]: he and co-workers systematically investigated the flow of water, solutes, and current in the lens, which is (in our opinion) a model of interdisciplinary research, combining theory, simulation, and measurements of many types [24, 25, 26, 27, 28, 29, 30, 32, 33, 34, 35, 36, 37, 38, 39, 40]. Computational models of the water flow in the lens were later developed in great detail [25, 41, 42] and compared to the more analytical models. These models have been extensively tested and we are fortunate that comprehensive reviews have been written of great value to newcomers to the field, particularly [43, 44] as well as [45, 46, 47, 48, 49, 43, 41, 44].

Since the pioneering work on the models of lens microcirculation system proposed by Mathias et al. [51, 21], numerous investigations have been carried out [52, 53, 23, 20, 19]. The microcirculation model has firstly relied on a combination of electrical resistance and current measurements and theoretical modeling [18, 54, 19]. More recently, in order to provide a better understanding the electric current flow and potential field, the detail structure of lens has been included [55, 41, 44, 43], describing the asymmetric biological properties of the lens and measurements of pressure have been made [47, 28]. Different types of fluid flow [56, 57] and transport properties of the ions have been introduced. Meanwhile, the lens model [55] has been extended to simulate age-related changes in lens physiology [58] and a variety of physiological processes [26, 59, 60, 61]. Reviews of current studies on micro-circulation in lens are most helpful [30, 26, 33]. Despite this large body of experimental and theoretical work, it is not completely clear how they are related to each other. In particular, it is not clear how the latest computational models are related to the pioneering work, and how theoretical analysis is related to experimental findings. In this paper, we will provide such a link.

Based on the microscale model for semipermeable membrane [62] and bidomain method [51], we construct a mathematical model to ensure that all interactions are included and treated consistently. Using asymptotic analysis, we derive a reduced model, which can be used to obtain most physiologically significant quantities except for the intracellular pressure. This simplified model can be further reduced to the model proposed by Mathias [51] with additional assumptions that Nernst potentials (that describe gradients of chemical potential of each ionic species) and conductance are constant in space. However, we will show that neither the Nernst potentials nor the conductance are constant. On the contrary, they vary significantly from the interior to the surface of the lens. Therefore, both of these quantities need to be

coupled as part of the solution.

Our model also shows explicitly that the intracellular pressure is decoupled from the rest of the variables. Evolution has chosen parameters so the intracellular pressure does not affect the other parameters of the lens in a significant way. They are robust to variations of intracellular pressure. The evolutionary advantage of this adaptation is not clear to us, but may be more obvious to other workers with a greater knowledge of clinical realities that show how the lens becomes diseased [63, 46, 48, 49]. Our simplified model suggests that all the quantities can be computed without knowing the intracellular pressure. On the other hand, we need to solve the full model to find the value of the intracellular pressure. Our model is also calibrated by experimental data and predicts the effects of gap junctions [28, 47] described by a ‘membrane’ permeability  $\kappa_{in}$ .

Our new results extend but do not fundamentally change previous work on the lens. We strengthen the view that the lens provides an osmotic pump to maintain the microcirculation necessary to sustain a living lens, for the life of the animal. We imagine that similar osmotic pumps create microcirculation in other cells and tissues of the body.

This paper is organized as following. The full model for micro-circulation of water and ions are proposed based on conservation laws in Section 2. In Section 3, we obtain the leading order model by identifying small parameters in the full model. Based on the boundary conditions and partial differential equation (PDE) analysis, a simplified version of the leading order model is proposed and compared with the existing models. The model calibration and simulation results are shown in Section 4. The conclusions and future work are given in Section 5.

## 2. Mathematical model

In this section, we present a 1-D spherical symmetric non-electro-neutral model for microcirculation of the lens with radius  $R$  by using the bidomain method [17]. The model deals with two types of flow: the circulation of water (hydrodynamics) and the circulation of ions (electrodynamics), generalizing previous bidomain models that deal only with electrodynamics. The model is mainly derived from laws of conservation of ions and water in the presence of membrane flow between intra and extracellular domains. We note that a similar approach may be useful in other tissues with narrow extracellular space, like the heart, cardiac muscle, and the central nervous system, including the cerebral cortex, ‘the brain’.

### 2.1. Water circulation

We assume

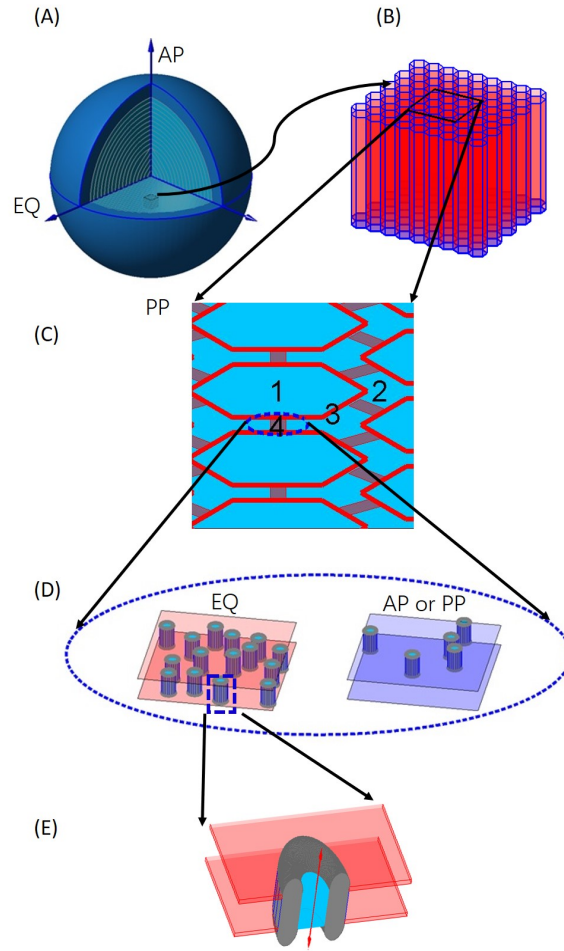


Figure 1: Schematic diagram of lens. (A) The sphere of the lens with three landmarks: anterior pole (AP), posterior pole (PP) and equator (EQ); (B) The control volume in the bidomain model; (C) The micro structure of the lens: 1. intracellular region 2. extracellular region 3. cell membrane 4. gap junction (connexions); (D) Distribution of the gap junctions between the cell membrane at EQ or AP and PP; (E) A single gap junction which allows the water and ions flows.

- the loss of intracellular water is only through membranes flowing into the extracellular space, vice versa [17];
- the trans-membrane water flux is proportional to the intra/extra-cellular hydrostatic pressure and osmotic pressure differences, i.e. Starling's law, classically applied to capillaries, here applied to membranes [64]. In a system like non-ideal ionic solutions in which 'everything interacts with everything else' [65, 66], this statement needs derivation as well as assertion. A complete, and rigorous derivation can be found in [62];
- in the rest of this paper, subscript  $l = in, ex$  denotes the intra-/extracellular space and superscript  $i = Na^+, K^+, Cl^-$  denotes the  $i$ th specie ion.

Then we obtain the following system for intra and extracellular velocities in domain  $\Omega = [0, R]$

$$\begin{aligned} \frac{1}{r^2} \frac{d}{dr} \left( r^2 \mathcal{M}_{ex} u_{ex} \right) \\ = -\mathcal{M}_v L_m (P_{ex} - P_{in} + \gamma_m k_B T (O_{in} - O_{ex})), \end{aligned} \quad (1a)$$

$$\frac{1}{r^2} \frac{d}{dr} (r^2 (\mathcal{M}_{ex} u_{ex} + \mathcal{M}_{in} u_{in})) = 0, \quad (1b)$$

where  $u_l$  and  $P_l$  are the velocity and pressure in the intracellular and extracellular space, respectively. And  $O_l$  is the osmotic pressure with definition

$$O_{ex} = \sum_i C_{ex}^i, \quad O_{in} = \sum_i C_{in}^i + \frac{A_{in}}{V_{in}},$$

where  $C_l^i$  is the concentration of  $i$ th specie ion in  $l$  space.  $\frac{A_{in}}{V_{in}}$  is the density of the permanent negative charged protein. In this paper, we assume the permanent negative charged protein is uniformly distributed within intracellular space with valence of  $\bar{z}$ . Here  $\mathcal{M}_l$  is the ratio of intracellular area ( $l = in$ ) and extracellular area ( $l = ex$ ),  $\mathcal{M}_v$  is the membrane area per volume unit,  $\gamma_m$  is the intracellular membrane reflectance,  $L_m$  is intracellular membrane hydraulic permeability,  $k_B$  is Boltzmann constant and  $T$  is temperature.

As we mentioned before, the intracellular space is a connected space, where water can flow from cell to cell through connexin proteins joining membranes of neighboring cells,, and the extracellular space is narrow with a high tortuosity. The intracellular velocity depends on the gradients of hydrostatic pressure and osmotic pressure [62, 41, 51], and the extracellular velocity is determined by the gradients of hydrostatic pressure and electric potential [41, 67],

$$u_{ex} = -\frac{\kappa_{ex}}{\mu} \tau_c \frac{d}{dr} P_{ex} - k_e \tau_c \frac{d}{dr} \phi_{ex}, \quad (2a)$$

$$u_{in} = -\frac{\kappa_{in}}{\mu} \left( \frac{d}{dr} P_{in} - \gamma_m k_B T \frac{d}{dr} O_{in} \right), \quad (2b)$$

where  $\phi_l$  is the electric potential in the  $l$  space,  $\tau_c$  is the tortuosity of extracellular region and  $\mu$  is the viscosity of water,  $k_e$  is introduced to describe the effect of electro osmotic flow,  $\kappa_l$  is the permeability of intracellular region ( $l = in$ ) and extracellular region ( $l = ex$ ), respectively.

Thanks to Eq. 2, Eq.1 can be treated as equation of hydraulic pressure. Due to the axis symmetry condition, homogeneous Neumann boundary conditions are used for pressure at  $r = 0$ . At the surface of lens  $r = R$ , we set the extracellular hydrostatic pressure to be zero and the intracellular velocity is consistent with Eq.2

$$\begin{cases} \frac{\partial P_{ex}}{\partial r} = \frac{\partial P_{in}}{\partial r} = 0, & \text{at } r = 0, \\ P_{ex} = 0, & \text{at } r = R, \\ -\frac{\kappa_{in}}{\mu} \left( \frac{d}{dr} P_{in} - \gamma_m k_B T \frac{d}{dr} O_{in} \right) \\ = L_s (P_{in} - \gamma_s k_B T (O_{in} - O_{ex})), & \text{at } r = R, \end{cases} \quad (3)$$

where  $\gamma_s$  is surface membrane reflectance and  $L_s$  is surface membrane hydraulic permeability.

## 2.2. Ion circulation

With similar assumptions, the conservation of ion concentration yields the following ion flux system

$$\frac{1}{r^2} \frac{d}{dr} (r^2 \mathcal{M}_{ex} J_{ex}^i) = \mathcal{M}_v j_m^i, \quad (4a)$$

$$\frac{1}{r^2} \frac{d}{dr} (r^2 (\mathcal{M}_{ex} J_{ex}^i + \mathcal{M}_{in} J_{in}^i)) = 0, \quad (4b)$$

The ion flux in the intracellular region  $J_{in}^i$  and ion flux in the extracellular region  $J_{ex}^i$  are defined as

$$J_{ex}^i = C_{ex}^i u_{ex} - D_{ex}^i \tau_c \frac{d}{dr} C_{ex}^i - D_{ex}^i \tau_c \frac{z^i e}{k_B T} C_{ex}^i \frac{d}{dr} \phi_{ex}, \quad (5a)$$

$$J_{in}^i = C_{in}^i u_{in} - D_{in}^i \frac{d}{dr} C_{in}^i - D_{in}^i \frac{z^i e}{k_B T} C_{in}^i \frac{d}{dr} \phi_{in}, \quad (5b)$$

where  $D_l^i$  is the diffusion coefficient of the  $i$ th specie ion in the  $l$  space. The Hodgkin-Huxley conductance formulation [68, 69] is used to describe the trans-membrane flux of ions across intracellular membrane and surface membrane

$$j_m^i = \frac{g^i}{ez^i} (\phi_{in} - \phi_{ex} - E^i), \quad (6a)$$

$$j_s^i = \frac{G^i}{ez^i} (\phi_{in} - \phi_{ex} - E^i) \quad (6b)$$

where  $E^i = \frac{k_B T}{ez^i} \log \left( \frac{C_{ex}^i}{C_{in}^i} \right)$  is the Nernst potential (an expression of the difference of chemical potential) of  $i$ th specie ion.

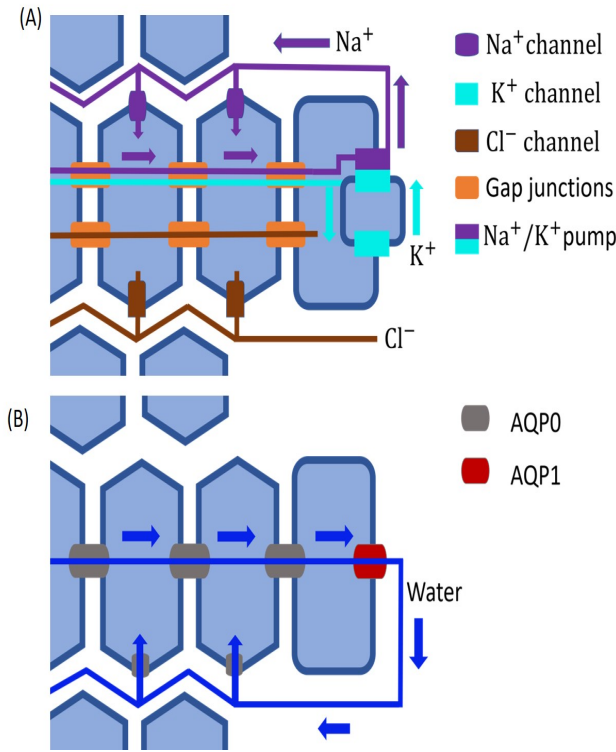


Figure 2: (A) Schematic diagram of ion circulation and the distributions of ion channels and pumps. The purple line represents the sodium circulation, the light green represents the potassium circulation and the brown line represents chloride circulation. The surface epithelial cells (dark black square) connect with the intracellular cells (light black hexagon) by the gap junctions (orange rectangle). The sodium and chloride ion channels are located on the intracellular membranes, while the potassium ion channel and sodium-potassium ATP pumps are found only on the surface membrane. (B) Schematic diagram of water circulation. Trans-membrane water transport is through AQP0 and AQP1 gap junctions. AQP0 gap junctions are located on the intracellular membranes, and AQP1 is on surface membrane.

In Eq. 6, the intracellular ion conductance  $g^i$  and surface ion conductance  $G^i$  depends on the ion channel distribution on the membrane (see Fig. 2). Based on previous work [51, 17, 41], we assume that (1) only  $\text{Na}^+$  and  $\text{Cl}^-$  can leak between intracellular and extracellular through ion channels inside the lens and (2)



that there is no trans-membrane flux for  $K^+$  between the extracellular and intracellular region, i.e.  $j_m^K = 0$ .

Similarly, homogeneous Neumann boundary conditions are used at  $r = 0$ . At  $r = R$ , the extracellular concentrations are fixed and Robin boundary conditions are used for intracellular concentrations due to the trans-membrane flux and pump,

$$\begin{cases} J_{ex}^i = J_{in}^i = 0, & \text{at } r = 0 \\ C_{ex}^i = C_o^i, J_{in}^i = j_s^i + a^i, & \text{at } r = R, \end{cases} \quad (7)$$

where  $a^i$  is active ion pump on the surface membrane. Here we only consider the sodium-potassium pump on the surface. The strength of the pump depends on the ion's concentration as in [29, 41],

$$a^{Na} = 3 \frac{I_p}{e}, \quad a^K = -2 \frac{I_p}{e}, \quad a^{Cl} = 0, \quad (8)$$

where

$$\begin{aligned} I_p = I_{max1} & \left( \frac{C_{in}^{Na}}{C_{in}^{Na} + K_{Na1}} \right)^3 \left( \frac{C_o^K}{C_o^K + K_{K1}} \right)^2 \\ & + I_{max2} \left( \frac{C_{in}^{Na}}{C_{in}^{Na} + K_{Na2}} \right)^3 \left( \frac{C_o^K}{C_o^K + K_{K2}} \right)^2. \end{aligned} \quad (9)$$

Due to the capacitance of the cell membrane, assumptions of exact charge neutrality can easily lead to paradoxes because they oversimplify Maxwell's equations by leaving out altogether the essential role of charge. We use the analysis of [70] and thus introduce a linear correction term replacing the charge neutrality condition [51, 41], without introducing significant error (See also [71]),

$$(1 - \eta) \left( \sum_i e z^i C_{ex}^i \right) = -\mathcal{M}_v C_m (\phi_{in} - \phi_{ex}), \quad (10a)$$

$$\eta \left( \sum_i e z^i C_{in}^i + \bar{z} e \frac{A_{in}}{V_{in}} \right) = \mathcal{M}_v C_m (\phi_{in} - \phi_{ex}), \quad (10b)$$

where  $\eta$  is the porosity of intracellular region and  $C_m$  is capacitance per unit area.

Multiplying each ion concentration equation in Eq. 4 with  $e z^i$  respectively, summing up and using Eq.10, the sodium equations are replaced by the following equations

$$\frac{1}{r^2} \frac{d}{dr} \left( r^2 \mathcal{M}_{ex} \left( \rho_{ex} u_{ex} - e \tau_c \sum_i D_{ex}^i z^i \frac{d}{dr} C_{ex}^i - \sigma_{ex} \frac{d}{dr} \phi_{ex} \right) \right)$$

$$= \mathcal{M}_v \left( g^m (\phi_{in} - \phi_{ex}) - \sum_i g^i E^i \right), \quad (11a)$$

$$\begin{aligned} & \frac{1}{r^2} \frac{d}{dr} \left( r^2 \mathcal{M}_{in} \left( \rho_{in} u_{in} - e \sum_i D_{in}^i z^i \frac{d}{dr} C_{in}^i - \sigma_{in} \frac{d}{dr} \phi_{in} \right) \right) \\ &= -\mathcal{M}_v \left( g^m (\phi_{in} - \phi_{ex}) - \sum_i g^i E^i \right), \end{aligned} \quad (11b)$$

with boundary conditions

$$\begin{cases} \frac{d\phi_{ex}}{dr} = \frac{d\phi_{in}}{dr} = 0, & \text{at } r = 0, \\ \phi_{ex} = 0, & \text{at } r = R, \\ \left( \rho_{in} u_{in} - e \sum_i D_{in}^i z^i \frac{d}{dr} C_{in}^i - \sigma_{in} \frac{d}{dr} \phi_{in} \right) \\ \quad = G^s \phi_{in} - \sum_i G^i E^i + I_p^\phi, & \text{at } r = R, \end{cases}$$

where  $\rho_{in} = \frac{\mathcal{M}_v C_m}{\eta} (\phi_{in} - \phi_{ex}) + |\bar{z}| e \frac{A_m}{V_{in}}$  and  $\rho_{ex} = \frac{\mathcal{M}_v C_m}{1-\eta} (\phi_{ex} - \phi_{in})$

$$g^m = \sum_i g^i, \quad G^s = \sum_i G^i, \quad I_p^\phi = e \sum_i z^i a^i.$$

In Eq. 11, we define the intracellular conductance  $\sigma_{in}$  and extracellular conductance  $\sigma_{ex}$  as

$$\sigma_{ex} = \frac{e^2 \tau_c}{k_B T} \left( \sum_i D_{ex}^i (z^i)^2 C_{ex}^i \right), \quad \sigma_{in} = \frac{e^2}{k_B T} \left( \sum_i D_{in}^i (z^i)^2 C_{in}^i \right).$$

It is obvious that system 11 might be derived using either Eq. 4 and Eq. 10. Therefore, we should drop either Eq. 4 or Eq. 10 when Eq. 11 is used.

### 2.3. Non-dimensionalization

Since lens circulation is driven by the sodium-potassium pump, it is natural to choose the characteristic velocity  $u_{in}^*$  by the pump strength  $a^{Na*}$

$$u_{in}^* = \frac{a^{Na*}}{O^*}. \quad (12)$$

where  $O^* = 2 (C_o^{Na} + C_o^K)$  is characteristic osmotic pressure. Using Eq. 1b, we obtain the scale of  $u_{ex}$  as

$$u_{ex}^* = \delta_0^{-1} u_{in}^*, \quad (13)$$

where  $\delta_0 = \frac{\mathcal{M}_{ex}}{\mathcal{M}_{in}}$ . With the characteristic values for  $\phi$ ,  $P$ ,  $C^i$ , chosen as  $\frac{k_B T}{e}$ ,  $\frac{\mu R u_{ex}^*}{\kappa_{ex} \tau_c}$ ,  $C_0^{Na} + C_0^K$ , we obtain the dimensionless system for lens problem as follows ( Detailed derivation is given in the appendix C.)

$$u_{ex} = -\frac{d}{dr} P_{ex} - \delta_1 \frac{d}{dr} \phi_{ex}, \quad (14a)$$

$$\delta_2 u_{in} = -\delta_3 \frac{d}{dr} P_{in} + \frac{d}{dr} O_{in}, \quad (14b)$$

$$\delta_4 \frac{1}{r^2} \frac{d}{dr} (r^2 u_{in}) = \delta_3 (P_{ex} - P_{in}) + (O_{in} - O_{ex}), \quad (14c)$$

$$u_{ex} = -u_{in}, \quad (14d)$$

$$\sum_i z^i C_{in}^i + \bar{z} \frac{A_{in}}{V_{in}} = \delta_6 (\phi_{in} - \phi_{ex}), \quad (14e)$$

$$\sum_i z^i C_{ex}^i = -\delta_7 (\phi_{in} - \phi_{ex}), \quad (14f)$$

$$\frac{1}{r^2} \frac{d}{dr} (r^2 J_{ex}^{Cl}) = \frac{\mathcal{M}_v^{ex}}{z^{Cl}} (\phi_{in} - \phi_{ex} - E^{Cl}), \quad (14g)$$

$$\frac{1}{r^2} \frac{d}{dr} (r^2 J_{in}^{Cl}) = -\frac{\delta_8}{r^2} \frac{d}{dr} (r^2 J_{ex}^{Cl}), \quad (14h)$$

$$\frac{1}{r^2} \frac{d}{dr} (r^2 J_{ex}^K) = 0, \quad (14i)$$

$$\frac{1}{r^2} \frac{d}{dr} (r^2 J_{in}^K) = 0, \quad (14j)$$

$$\begin{aligned} & \frac{1}{r^2} \frac{d}{dr} \left( r^2 \left( P_{ex} \rho_{ex} u_{ex} - \sum_i D_{ex}^i z^i \frac{d}{dr} C_{ex}^i - \sigma_{ex} \frac{d}{dr} \phi_{ex} \right) \right) \\ &= \mathcal{M}_v^{ex} (2 (\phi_{in} - \phi_{ex}) - E^{Na} - E^{Cl}), \end{aligned} \quad (14k)$$

$$\begin{aligned} & \frac{1}{r^2} \frac{d}{dr} \left( r^2 \left( P_{in} \rho_{in} u_{in} - \sum_i D_{in}^i z^i \frac{d}{dr} C_{in}^i - \sigma_{in} \frac{d}{dr} \phi_{in} \right) \right) \\ &= -\frac{\delta_8}{r^2} \frac{d}{dr} \left( r^2 \left( P_{ex} \rho_{ex} u_{ex} - \sum_i D_{ex}^i z^i \frac{d}{dr} C_{ex}^i - \sigma_{ex} \frac{d}{dr} \phi_{ex} \right) \right), \end{aligned} \quad (14l)$$

with homogeneous Neumann boundary conditions at  $r = 0$  and following boundary conditions at  $r = 1$

$$\left\{ \begin{array}{l} P_{ex} = 0, \\ \delta_5 u_{in} = \delta_3 P_{in} - (O_{in} - O_{ex}), \\ C_{ex}^K = C_o^K, \quad J_{in}^K = \frac{R_s}{z_K} (\phi_{in} - E^K) - a^K, \\ C_{ex}^{Cl} = \tilde{C}_o^{Na} + \tilde{C}_o^K + \delta_7 (\tilde{\phi}_{in} - \tilde{\phi}_{ex}), \quad J_{in}^{Cl} = 0, \\ \phi_{ex} = 0, \\ P e_{in} \rho_{in} u_{in} - \sum_i D_{in}^i z^i \frac{d}{dr} C_{in}^i - \sigma_{in} \frac{d}{dr} \phi_{in} \\ = \frac{R_s}{z_K} (\phi_{in} - E^K) + I_p^\phi, \end{array} \right.$$

where

$$\rho_{in} = \rho_0 + \delta_6 (\phi_{in} - \phi_{ex}), \quad \rho_0 = |\bar{z}| \frac{A_{in}}{V_{in}}, \quad (15a)$$

$$\rho_{ex} = \delta_7 (\phi_{ex} - \phi_{in}), \quad (15b)$$

$$\sigma_l = \sum_i D_l^i (z^i)^2 C_l^i, \quad (15c)$$

$$E^i = \frac{1}{z^i} \log \left( \frac{C_{ex}^i}{C_{in}^i} \right), \quad (15d)$$

$$I_p^\phi = \frac{I_p R}{e D_{in}^* C^*}. \quad (15e)$$

$$J_l^i = P e_l C_l^i u_l - D_l^i \left( \frac{d}{dr} C_l^i + z^i C_l^i \frac{d}{dr} \phi_l \right). \quad (15f)$$

### 3. Simplified model

The full model given by system 14 with boundary condition 15 is a coupled nonlinear system. In this section, we present a simplified version of the full model which captures the main features of the lens circulation. We first obtain the leading order model by identify the small parameters. And then by using boundary conditions and theoretical analysis, the leading order model with is further simplified as only one PDE with serial algebra equations.

According to those dimensionless parameters presented in the appendix B, we identify the scale of the

parameters as follows

$$\begin{aligned} \{\delta_1, \delta_8\} &\subset O(\epsilon), \quad \{\delta_0, \delta_3\} \subset O(\epsilon^2), \\ \{\delta_2, \delta_4, \delta_5, \delta_6, \delta_7\} &\subset o(\epsilon^2). \end{aligned} \quad (16)$$

If we denote  $\delta_9 = D_l^{Cl} - D_l^K$  and  $\delta_{10} = D_l^{Cl} - D_l^{Na}$ ,  $l = in, ex$ , it yields

$$\delta_9 = O(\epsilon^2), \quad \delta_{10} = O(\epsilon). \quad (17)$$

### 3.1. A priori estimation

In this section, we provide the priori estimation of the  $J_{in}^{Cl}$  as follows. By using the homogeneous Neumann boundary condition at  $r = 0$  and Eq. 14l yields

$$\begin{aligned} \frac{d}{dr}\phi_{in} &= \frac{1}{\sigma_{in}} \left( Pe_{in}\rho_{in}u_{in} + \delta_9 \frac{d}{dr}C_{in}^K + \delta_{10} \frac{d}{dr}C_{in}^{Na} \right) \\ &+ \frac{\delta_8}{\sigma_{in}} \left( Pe_{ex}\rho_{ex}u_{ex} + \delta_9 \frac{d}{dr}C_{ex}^K + \delta_{10} \frac{d}{dr}C_{ex}^{Na} - \sigma_{ex} \frac{d}{dr}\phi_{ex} \right). \end{aligned} \quad (18)$$

From Eq. 18, since  $Pe_{in} = O(\epsilon)$  and order of  $\delta_8, \delta_9, \delta_{10}$  in Eqs. 16-17, we obtain that

$$\frac{d}{dr}\phi_{in} = O(\epsilon). \quad (19)$$

Meanwhile, from Eq. 14b we can have

$$\frac{d}{dr}O_{in} = O(\epsilon^2). \quad (20)$$

and in the Eq. 14e, we know

$$\frac{d}{dr}C_{in}^{Cl} = \frac{d}{dr} \left( C_{in}^{Na} + C_{in}^K \right) + o(\epsilon^2), \quad (21)$$

With Eqs. 20-21 and  $\frac{A_{in}}{V_{in}}$  is constants, we obtain

$$\frac{d}{dr}C_{in}^{Cl} = O(\epsilon^2). \quad (22)$$

Furthermore, using Eq. 14d and boundary conditions for  $C_{ex}^{Cl}$  in Eq. 15 yieldds

$$C_{in}^{Cl} = C_o^{Na} + C_o^K - \frac{1 + |\bar{z}|}{2} \frac{A_{in}}{V_{in}} + O(\epsilon^2). \quad (23)$$

From the experimental setting of lens [51, 55, 41], we assume that

$$C_o^{Na} + C_o^K - \frac{1 + |\bar{z}|}{2} \frac{A_{in}}{V_{in}} = O(\epsilon). \quad (24)$$

Therefore,

$$C_{in}^{Cl} = O(\epsilon). \quad (25)$$

In all, we claim that

$$\begin{aligned} J_{in}^{Cl} &= Pe_{in} C_{in}^{Cl} u_{in} - D_{in}^{Cl} \left( \frac{d}{dr} C_{in}^{Cl} + z^{Cl} C_{in}^{Cl} \frac{d}{dr} \phi_{in} \right) \\ &= O(\epsilon^2). \end{aligned} \quad (26)$$

By dropping the terms involving these small parameters, the leading order of water circulation system 14a-14d is as follows,

$$u_{ex}^0 = -\frac{d}{dr} P_{ex}^0 - \delta_1 \frac{d}{dr} \phi_{ex}^0, \quad (27a)$$

$$\frac{d}{dr} O_{in}^0 = 0, \quad (27b)$$

$$O_{in}^0 - O_{ex}^0 = 0, \quad (27c)$$

$$u_{ex}^0 = -u_{in}^0, \quad (27d)$$

where the superscript '0' denotes the leading order approximation. From Eq. 27, we deduce  $O_{ex}^0 = O_{in}^0$  are constants, and the intracellular and extracellular flow are counterflow. And the total charge in the leading order systems are neutral

$$\sum_i z^i C_{in}^{i,0} + \bar{z} \frac{A_{in}}{V_{in}} = 0, \quad (28a)$$

$$\sum_i z^i C_{ex}^{i,0} = 0. \quad (28b)$$

Combining constant osmotic pressure and charge neutrality yields

$$O_{ex}^0(r) = O_{in}^0(r) = 2 \left( C_{ex}^{Na,0}(1) + C_{ex}^{K,0}(1) \right), \quad (29a)$$

$$\frac{dC_{in}^{Cl,0}}{dr} = \frac{dC_{ex}^{Cl,0}}{dr} = 0, \quad (29b)$$

which means  $C_{in}^{Cl,0}$  and  $C_{ex}^{Cl,0}$  are constants and

$$\frac{dC_l^{Na,0}}{dr} = -\frac{dC_l^{K,0}}{dr}, \quad l \in \{in, ex\}. \quad (30)$$

And the leading order of potassium and chloride concentrations satisfy

$$\frac{1}{r^2} \frac{d}{dr} \left( r^2 J_{in}^{K,0} \right) = 0, \quad (31a)$$

$$\frac{1}{r^2} \frac{d}{dr} \left( r^2 J_{ex}^{K,0} \right) = 0 \quad (31b)$$

$$\frac{1}{r^2} \frac{d}{dr} \left( r^2 J_{ex}^{Cl,0} \right) = \frac{\mathcal{M}_{\vartheta}^{ex}}{z^{Cl}} \left( \phi_{in}^0 - \phi_{ex}^0 - E^{Cl,0} \right) \quad (31c)$$

$$\frac{1}{r^2} \frac{d}{dr} \left( r^2 J_{in}^{Cl,0} \right) = -\frac{1}{r^2} \frac{d}{dr} \left( r^2 \delta_8 J_{ex}^{Cl,0} \right), \quad (31d)$$

where  $J_l^{i,0} = Pe_l C_l^{i,0} u_l^0 - D_l^i \left( \frac{d}{dr} C_l^{i,0} + z^i C_l^{i,0} \frac{d}{dr} \phi_l^0 \right)$  with  $i = K, Cl$  and  $l = in, ex$ ,  $E^{Cl,0} = \frac{1}{z^{Cl}} \log \left( \frac{C_{ex}^{Cl,0}}{C_{in}^{Cl,0}} \right)$ .

For the electric potential, using the homogeneous Neumann boundary condition at  $r = 0$  and Eqs. 29a-30, 141 yields

$$\begin{aligned} \frac{d}{dr} \phi_{in} &= \frac{1}{\sigma_{in}} \left( Pe_{in} \rho_{in} u_{in} + \delta_9 \frac{d}{dr} C_{in}^K + \delta_{10} \frac{d}{dr} C_{in}^{Na} \right) \\ &+ \frac{\delta_8}{\sigma_{in}} \left( Pe_{ex} \rho_{ex} u_{ex} + \delta_9 \frac{d}{dr} C_{ex}^K + \delta_{10} \frac{d}{dr} C_{ex}^{Na} - \sigma_{ex} \frac{d}{dr} \phi_{ex} \right). \end{aligned} \quad (32)$$

At the same time, based on the intracellular equation of potassium Eq. 14j the homogeneous Neumann boundary condition at  $r = 0$  and Eqs. 29a-30, we have

$$D_{in}^K \frac{d}{dr} C_{in}^K = \left( Pe_{in} C_{in}^K u_{in} - D_{in}^K z^K C_{in}^K \frac{d}{dr} \phi_{in} \right) \quad (33)$$

Substituting Eq. 32 into Eq. 33 yields

$$\begin{aligned} &\left( 1 - z^K C_{in}^K \frac{\delta_{10}}{\sigma_{in}} \right) D_{in}^K \frac{dC_{in}^K}{dr} \\ &= \left( \left( 1 - z^K D_{in}^K \frac{\rho_{in}}{\sigma_{in}} \right) Pe_{in} u_{in} + z^K D_{in}^K \frac{\delta_8 \sigma_{ex}}{\sigma_{in}} \frac{d\phi_{ex}}{dr} \right) C_{in}^K \\ &+ O(\epsilon^2), \end{aligned} \quad (34)$$

where we used that fact that  $\rho_{ex} = o(\epsilon^2)$ ,  $\delta_9 = O(\epsilon^2)$  and  $\frac{dC_l^K}{dr} = -\frac{dC_l^{Na}}{dr} + O(\epsilon^2)$ ,  $l \in \{in, ex\}$ . Since

$Pe_{in} = O(\epsilon)$ , and  $\delta_8 = O(\epsilon)$ , in Eq. 34, we claim

$$\frac{dC_{in}^K}{dr} = O(\epsilon). \quad (35)$$

Combining Eqs. 32 and 35 yields the leading order approximation of intracellular potential

$$\frac{d}{dr}\phi_{in}^0 = \frac{1}{\sigma_{in}^0}Pe_{in}\rho_0u_{in}^0 - \frac{\delta_8}{\sigma_{in}^0}\sigma_{ex}^0\frac{d}{dr}\phi_{ex}^0 = O(\epsilon), \quad (36)$$

where  $\sigma_{in}^0 = \sum_i D_{in}^i(z^i)^2 C_{in}^{i,0}$ ,  $\sigma_{ex}^0 = \sum_i D_{ex}^i(z^i)^2 C_{ex}^{i,0}$ .

Similarly, the leading order approximation of extracellular potential is

$$\begin{aligned} & -\frac{1}{r^2}\frac{d}{dr}\left(r^2\left(\delta_{10}\frac{d}{dr}C_{ex}^{Na,0} + \sigma_{ex}^0\frac{d}{dr}\phi_{ex}^0\right)\right) \\ & = \mathcal{M}_v^{ex}\left(2\left(\phi_{in}^0 - \phi_{ex}^0\right) - E^{Na,0} - E^{Cl,0}\right), \end{aligned} \quad (37)$$

where  $E^{Na,0} = \frac{1}{z^{Na}}\log\left(\frac{C_{ex}^{Na,0}}{C_{in}^{Na,0}}\right)$ .

To summarize, the leading order approximation of system 14-15 is given by, in domain  $\Omega = [0, 1]$

$$u_{ex}^0 = -\frac{d}{dr}P_{ex}^0 - \delta_1\frac{d}{dr}\phi_{ex}^0, \quad (38a)$$

$$\frac{d}{dr}O_{in}^0 = 0, \quad (38b)$$

$$O_{in}^0 - O_{ex}^0 = 0, \quad (38c)$$

$$u_{ex}^0 = -u_{in}^0, \quad (38d)$$

$$\sum_i z^i C_{in}^{i,0} + \bar{z}\frac{A_{in}}{V_{in}} = 0, \quad (38e)$$

$$\sum_i z^i C_{ex}^{i,0} = 0, \quad (38f)$$

$$\frac{1}{r^2}\frac{d}{dr}\left(r^2J_{in}^{K,0}\right) = 0, \quad (38g)$$

$$\frac{1}{r^2}\frac{d}{dr}\left(r^2J_{ex}^{K,0}\right) = 0, \quad (38h)$$

$$\frac{1}{r^2}\frac{d}{dr}\left(r^2J_{ex}^{Cl,0}\right) = \frac{\mathcal{M}_v^{ex}}{z^{Cl}}\left(\phi_{in}^0 - \phi_{ex}^0 - E^{Cl,0}\right), \quad (38i)$$

$$\frac{1}{r^2}\frac{d}{dr}\left(r^2J_{in}^{Cl,0}\right) = -\frac{1}{r^2}\frac{d}{dr}\left(r^2\delta_8J_{ex}^{Cl,0}\right), \quad (38j)$$

$$\frac{d}{dr}\phi_{in}^0 = \frac{1}{\sigma_{in}^0}Pe_{in}\rho_0u_{in}^0 - \frac{\delta_8}{\sigma_{in}^0}\sigma_{ex}^0\frac{d}{dr}\phi_{ex}^0, \quad (38k)$$



$$\begin{aligned}
& -\frac{1}{r^2} \frac{d}{dr} \left( r^2 \left( \delta_{10} \frac{d}{dr} C_{ex}^{Na,0} + \sigma_{ex}^0 \frac{d}{dr} \phi_{ex}^0 \right) \right) \\
& = \mathcal{M}_v^{ex} \left( 2 \left( \phi_{in}^0 - \phi_{ex}^0 \right) - E^{Na,0} - E^{Cl,0} \right),
\end{aligned} \tag{38l}$$

with boundary conditions at  $r = 1$

$$\left\{ \begin{aligned}
& P_{ex}^0 = 0, C_{ex}^{Cl,0} = C_o^{Na} + C_o^K, C_{ex}^{K,0} = C_o^K, \\
& Pe_{in} C_{in}^{K,0} u_{in}^0 - D_{in}^K \left( \frac{d}{dr} C_{in}^{K,0} + z^K C_{in}^{K,0} \frac{d}{dr} \phi_{in}^0 \right) \\
& = \frac{R_s}{z_K} \left( \phi_{in}^0 - E^{K,0} \right) - a^K, \\
& Pe_{in} \rho_0 u_{in}^0 + \delta_{10} \frac{d}{dr} C_{in}^{Na,0} - \sigma_{in} \frac{d}{dr} \phi_{in}^0 \\
& = \frac{R_s}{z_K} \left( \phi_{in}^0 - E^{K,0} \right) + I_p^e, \\
& \phi_{ex}^0 = 0.
\end{aligned} \right. \tag{39}$$

In the following, we will further simplify Eqs. 38-39 and obtain the relationships between  $\phi_{ex}^0$  and other leading order variables by using assumptions concerning the boundary conditions.

### 3.2. Relation between $\phi_{in}^0$ and $\phi_{ex}^0$

Combining Eqs. 38a, 38d and 38k, and integrating with respect to  $r$  yields the relation between  $\phi_{in}^0$  and  $\phi_{ex}^0$  as

$$\begin{aligned}
\phi_{in}^0(r) & = \left( \frac{Pe_{in} \rho_0 \delta_1}{\sigma_{in}^0} - \frac{\delta_8 \sigma_{ex}^0}{\sigma_{in}^0} \right) \phi_{ex}^0(r) \\
& + \frac{Pe_{in} \rho_0}{\sigma_{in}^0} P_{ex}^0(r) + \phi_{in}^0(1).
\end{aligned} \tag{40}$$

where we used the boundary conditions  $\phi_{ex}^0(1) = P_{ex}^0(1) = 0$ .

### 3.3. Relation between $P_{ex}^0$ and $\phi_{ex}^0$

By the homogeneous Neumann boundary condition on  $r = 0$  and Eq. 38j, we have

$$J_{in}^{Cl,0} + \delta_8 J_{ex}^{Cl,0} = 0. \tag{41}$$

By Eq. 29b, we can divide Eq. 41 by  $C_{ex}^{Cl,0}$  on both sides, we get

$$\begin{aligned} & \left( Pe_{in} \frac{C_{in}^{Cl,0}}{C_{ex}^{Cl,0}} u_{in}^0 - D_{in}^{Cl} z^{Cl} \frac{C_{in}^{Cl,0}}{C_{ex}^{Cl,0}} \frac{d\phi_{in}^0}{dr} \right) \\ & + \delta_8 \left( Pe_{ex} u_{ex}^0 - D_{ex}^{Cl} z^{Cl} \frac{d\phi_{ex}^0}{dr} \right) = 0. \end{aligned} \quad (42)$$

Base on the charge neutrality Eq. 28, constant osmotic pressure Eq. 29a and parameters in Appendix B, we denotes

$$\delta_{11} = \frac{C_{in}^{Cl,0}}{C_{ex}^{Cl,0}} = \frac{C_o^{Na} + C_o^K - \frac{1+|z|}{2} \frac{A_{in}}{V_{in}}}{C_o^{Cl,0}} = O(\epsilon). \quad (43)$$

Then combining the Eqs. 36 and  $Pe_{in} = O(\epsilon)$ , Eq. 42 yields the following equation by omitting the higher order terms

$$Pe_{ex} u_{ex}^0 - D_{ex}^{Cl} z^{Cl} \frac{d\phi_{ex}^0}{dr} = 0. \quad (44)$$

Finally, by using the boundary condition, we have the relation between extracellular pressure and electric potential as

$$p_{ex}^0 = \frac{D_{ex}^{Cl} - Pe_{ex} \delta_1}{Pe_{ex}} \phi_{ex}^0. \quad (45)$$

### 3.4. Expression of $E^{Na}$

Based on potassium equation and relation in Eqs. 40 and 45, we have expression for  $C_{in}^K$  and  $C_{ex}^K$  as

$$C_{ex}^{K,0} = C_o^{K,0} \exp \left( - \left( 1 + \frac{D_{ex}^{Cl}}{D_{ex}^K} \right) \phi_{ex}^0 \right), \quad (46a)$$

$$\begin{aligned} C_{in}^{K,0} &= C_{in}^{K,0}(1) \exp \left( \left( \frac{Pe_{in} D_{ex}^{Cl}}{Pe_{ex} D_{in}^K} - \frac{Pe_{in} D_{ex}^{Cl} \rho_0}{Pe_{ex} \sigma_{in}^0} \right) \phi_{ex}^0 \right) \\ &\exp \left( \left( \frac{\delta_9 \sigma_{ex}^0}{\sigma_{in}^0} \right) \phi_{ex}^0 \right), \end{aligned} \quad (46b)$$

where

$$C_{in}^{K,0}(1) = C_o^{K,0} \exp \left( \frac{a^K}{R_s} - \phi_{in}(1) \right). \quad (47)$$

Based on Eq. 28, we can get

$$\begin{aligned} E^{Na,0} &= \frac{1}{z^{Na}} \log \left( \frac{C_{ex}^{Na,0}}{C_{in}^{Na,0}} \right) \\ &= \frac{1}{z^{Na}} \log \left( \frac{C_{ex}^{Cl,0} - C_{ex}^{K,0}}{C_{in}^{Cl,0} + |z| \frac{A_{in}}{V_{in}} - C_{in}^{K,0}} \right). \end{aligned} \quad (48)$$

### 3.5. Extracellular electric potential system

By Eqs. 40 and 45, we have  $\phi_{in}$  as

$$\phi_{in}^0(r) = \left( \frac{D_{ex}^{Cl} P e_{in} \rho_0}{\sigma_{in}^0 P e_{ex}} - \frac{\delta_9 \sigma_{ex}^0}{\sigma_{in}^0} \right) \phi_{ex}^0(r) + \phi_{in}^0(1), \quad (49)$$

The value  $\phi_{in}^0(1)$  is determined by the boundary condition of  $\phi_{in}^0$  in Eq. 39, where

$$-\mathcal{M}_v^{in} \int_0^1 \left( 2 \left( \phi_{in}^0 - \phi_{ex}^0 \right) - E^{Na,0} - E^{Cl,0} \right) s^2 ds = a^{Na}. \quad (50)$$

where we use

$$a^{Na} = -a^K + I_p^\phi, \quad \frac{R_s}{zK} \left( \phi_{in} - E^K \right) = -a^K.$$

To summarize, we obtained the simplified model of system 38-39 as follows

$$\begin{aligned} & -\frac{1}{r^2} \frac{d}{dr} \left( r^2 \left( \delta_{10} \frac{d}{dr} C_{ex}^{Na,0} + \sigma_{ex}^0 \frac{d}{dr} \phi_{ex}^0 \right) \right) \\ & = \mathcal{M}_v^{ex} \left( 2 \left( \phi_{in}^0 - \phi_{ex}^0 \right) - E^{Na,0} - E^{Cl,0} \right), \end{aligned} \quad (51a)$$

$$\phi_{in}^0(r) = \left( \frac{D_{ex}^{Cl} P e_{in} \rho_0}{\sigma_{in}^0 P e_{ex}} - \frac{\delta_9 \sigma_{ex}^0}{\sigma_{in}^0} \right) \phi_{ex}^0(r) + \phi_{in}^0(1), \quad (51b)$$

$$\begin{aligned} & -\mathcal{M}_v^{in} \int_0^1 \left( 2 \left( \phi_{in}^0 - \phi_{ex}^0 \right) - E^{Na,0} - E^{Cl,0} \right) s^2 ds, \\ & = a^{Na} \end{aligned} \quad (51c)$$

$$u_{ex}^0 = -\frac{d}{dr} P_{ex}^0 - \delta_1 \frac{d}{dr} \phi_{ex}^0, \quad (51d)$$

$$u_{in}^0 = -u_{ex}^0 \quad (51e)$$

$$C_{ex}^{K,0} = C_0^{K,0} \exp \left( - \left( 1 + \frac{D_{ex}^{Cl}}{D_{ex}^K} \right) \phi_{ex}^0 \right), \quad (51f)$$

$$\begin{aligned} C_{in}^{K,0} &= C_{in}^{K,0}(1) \exp \left( \left( \frac{P e_{in} D_{ex}^{Cl}}{P e_{ex} D_{in}^K} - \frac{P e_{in} D_{ex}^{Cl} \rho_0}{P e_{ex} \sigma_{in}^0} \right) \phi_{ex}^0 \right) \\ & \exp \left( \left( \frac{\delta_9 \sigma_{ex}^0}{\sigma_{in}^0} \right) \phi_{ex}^0 \right), \end{aligned} \quad (51g)$$

$$C_{ex}^{Na,0} = C_{ex}^{Cl,0} - C_{ex}^{K,0}, \quad (51h)$$

$$C_{in}^{Na,0} = C_{in}^{Cl,0} + \bar{z} \frac{A_{in}}{V_{in}} - C_{in}^{K,0}, \quad (51i)$$

$$C_{in}^{Cl,0} = C_o^{Na,0} + C_o^{K,0} - \frac{1 + |\bar{z}|}{2} \frac{A_{in}}{V_{in}}, \quad (51j)$$

$$C_{ex}^{Cl,0} = C_o^{Na,0} + C_o^{K,0}, \quad (51k)$$

$$P_{ex}^0 = \frac{D_{ex}^{Cl} - Pe_{ex}\delta_1}{Pe_{ex}}\phi_{ex}^0. \quad (51l)$$

with boundary conditions

$$\begin{cases} \frac{d\phi_{ex}^0}{dr} = 0, & \text{at } r = 0, \\ \phi_{ex}^0 = 0, & \text{at } r = 1. \end{cases} \quad (52)$$

**Remark 3.1.** Under the same assumptions in [51], for example, uniform diffusion constants for all ions, constant Nernst potential, our simplified model system 51 recovers the model proposed by Mathias. The main contribution here is that we remove the assumptions that Nernst potentials and effective conductance should be constants. By using the relationships between ions concentrations and external potential, we obtain the space dependent Nernst potential which yields a much better approximation to the full model (see Fig. 4).

#### 4. Results and discussion

In this section, we present numerical simulations using both the full and simplified models. Finite Volume Method [70] is used in order to preserve mass conservation of ions. The convex iteration [72] is employed to solve the nonlinear coupled system. The numerical algorithm is implemented in Matlab.

##### 4.1. Model calibration: membrane conductance effects intracellular hydrostatic pressure

In this section, we first calibrate the full model by the comparing with the experimental data to study effect of connexin to intracellular hydrostatic pressure.

Intracellular hydrostatic pressure is an important physiological quantity [63]. In the paper [28, 47], the authors showed the connexin (gap junction) conductance play an important role in the microcirculation of lens. It is said that if the intracellular conductance  $\frac{\kappa_{in}}{\mu_{in}}$  in lenses is approximately doubled, the hydrostatic pressure gradient in the lenses should become approximately half of the original one. In this section, we calibrate our model. We choose a value of the intracellular conductance ( $\frac{\kappa_{in}}{\mu_{in}}$ ) that correctly calculates the experimental results in the [28, 47].

In Figure 3 (A), the value  $\kappa_{in}^w = 4.6830 \times 10^{-20} / m^2$  (black line) yields a good approximation to experimental data (black makers). When the conductivity of the connexins is doubled, to parameter value  $\kappa_{in}$  to be  $2\kappa_{in}^w$  (in the lens of mice Cx46 KI lens) as in the experiments [28, 47], where doubled the conductivity of the connexins by using Cx46 KI mice lens, our model (black dot) can also match the experimental data

(red markers): the intracellular hydrostatic pressure drops to half. This result shows that our full model can correctly predict the effect of permeability of membrane on hydrostatic pressure.

Interestingly, panels (B)-(D) it shows that other intracellular quantities and extracellular ones (appendix) are insensitive to increases in the permeability by a factor of twenty, even to  $20\kappa_{in}^w$ . The reason for this can be explained by using our simplified the system 51. If the variation of intracellular conductance still keep the  $\delta_2$  to be a small quantity in the dimensionless system 14, our simplified model will be still valid. In the simplified model, All the quantities except intracellular hydrostatic pressure are related to the extracellular electric potential. However, the extracellular electric potential will not be effected by the change of the intracellular conductance, since Eq. 51a not involves intracellular conductance.

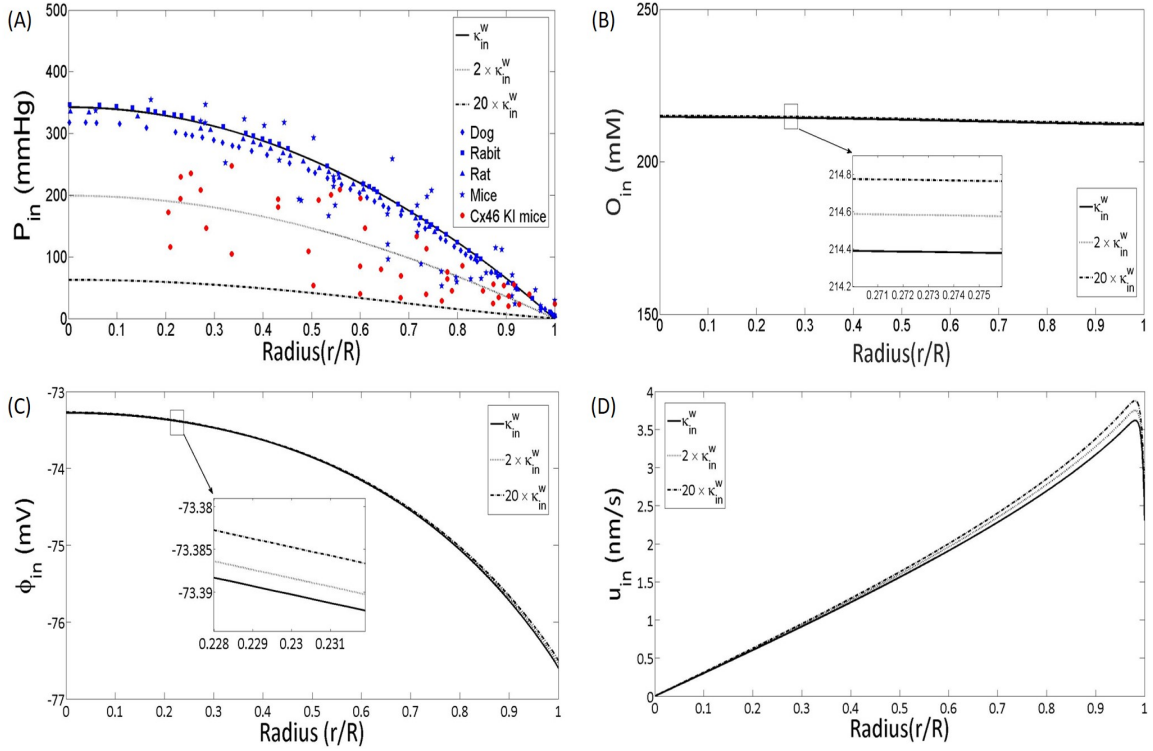


Figure 3: Comparison between different  $\kappa_{in}$ . The experimental data of dog, rabbit, rat come from paper [47]. Mice and Cx46 KI mice come from paper [28]. According to paper [28], the Cx46 KI mice lens has twice the number density of lens gap junction channels compared to mice. The parameter  $\kappa_{in}^w = 4.6830 \times 10^{-20} / \text{m}^2$  and radius is written in dimensionless units for different species

#### 4.2. Full model vs simplified model

In this section, we compare the full model 14-15 with the simplified model 51 and Mathias model in [51]. The numerical results of full model (Black lines) in Figure 4 (A-C) suggest that the variations intracellular electric potential, extracellular conductance and Nernst potential of  $\text{Cl}^-$  are rather small. The

assumption of constant values for those variables ( potential, extracellular conductance, and Nernst, i.e. chemical potential of  $\text{Cl}^-$  ) in the Mathias's model (shown as red dash-dot lines) is reasonable. However, the Nernst potentials of sodium and potassium (Figure 4 (D-E)) have large variations, because of the effect of Sodium-potassium pump. Our simplified model (black dash lines) describes these variations with small errors. The comparisons for extracellular pressure, velocity, and potential (Figure 4 (F-H)) confirm that our simplified model yields good approximations to the full model.

## 5. Conclusion

In this paper, we propose a bidomain model to study the microcirculation of lens. We include a capacitor in the representation of the membrane and so our model is consistent with classical electrodynamics. Consistency produces a linear correction term in the classical charge neutrality equation. This full model is calibrated by comparing with the experiment studying effect of connexin on hydrostatic pressure. It shows that only by changing intracellular membrane conductance (strength of connexin), our model could match the two experimental results with different connexin very well. Our model is capable of making prediction to the circulation of lens. Furthermore, the numerical simulations show that the velocity, potential, osmotic pressure in the intra and extra cellular are not sensitive to increasing conductance.

Based on the asymptotic analysis, we proposed a simplified model, which allows us to obtain a deep understanding of the physical process without making unrealistic assumptions. Our results showed that the simplified model is a good approximation of the full model where Nernst potentials and conductivity vary significantly inside the lens.

Our model allows calculation of variables that determine the role and life of the lens as an organ. Particularly important are the factors that determine the transparency of the lens, since that is the main function of the organ. The dependence of the size of the extracellular space, and thus the pressure in the extracellular and intracellular spaces and the difference between those two, is likely to be an important determinant of transparency. One imagines that swelling of the extracellular space will scatter light, particularly because the swelling is likely to be irregular (in a way our model does not yet capture). Changes in the Osmolarity (i.e., activity of water estimated by the total concentration of solutes) is likely to be important as well.

This hydrodynamic bidomain model can point the way to dealing with other cells, tissues, and organs in which current flow, water flow, and cell volume changes are important. These include the kidney, the central nervous system (where the narrow extracellular space poses many of the biological problems facing

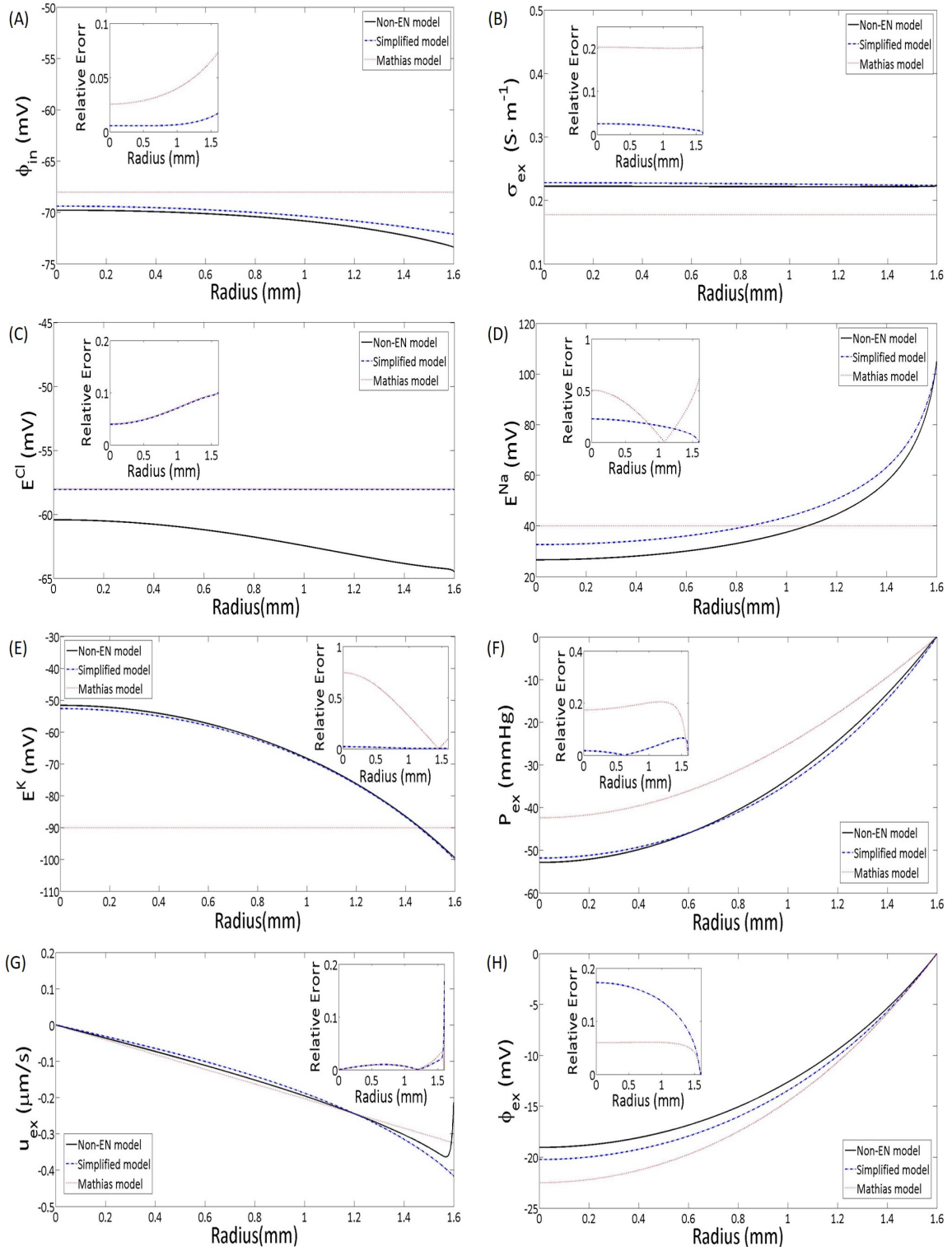


Figure 4: Comparison of electro-neutral and simplified and Mathias's model in [51].

the lens), the t-tubular system of skeletal and much cardiac muscle and so on. We show that a mathematically well defined model can deal with the reality of biological structure and its complex distribution of channels, etc.

Conservation laws applied to simplified structures are enough to provide quite useful results, as they were in three dimensional electrical problems of cells of various geometries [16] and syncytia [3]-[23]. The exact results are analyzed with perturbation methods, described in general in [73] and these methods allow dramatic simplifications without introducing large or even significant errors. It is as if evolution chose systems in which parameters and structures allow simple results, in which parameters can control biological function robustly.

Of course, we only point the way. Additional compartments and additional structural complexity will surely be needed to deal with the workings of evolution. But these can be handled in a mathematically defined way, yielding approximate results with clear physical and biological interpretation. Combining the multi-domain model and membrane potential dependent conductance, one can model depolarization induced by extra potassium in lens [53, 55] and cortical spreading depression (CSD) problem [74, 75, 71]. The ultimate goals will be (i) to provide as much precision in the mathematics and physics as we can, starting from first principles [62]; (ii) to provide a general basis for treatments of convection in other tissues that involve microcirculation. Computational models of these are not in hand, and may be hard to construct, since so little is known of those systems compared to the lens. With what we have learned here, we hope a general mathematical approach and model of the type we present here may be constructed and helpful in other systems with narrow extracellular spaces that are likely to need microcirculation to augment diffusion, like cardiac and skeletal muscle, kidney, liver, epithelia, and the extracellular space of the brain.

### **Author Contributions**

Y.Z, S.X, and H.H did the model derivations and carried out the numerical simulations. R.S.E and H.H designed the study, coordinated the study, and commented on the manuscript. All authors gave final approval for publication.

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## Appendix A. Model Parameters

Parameters	Mathias [51]	Malcolm [55]	Parameters	Mathias [51]	Malcolm [55]
$R$	$1.6 \times 10^{-3} \text{ m}$	$1.6 \times 10^{-3} \text{ m}$	$L_m$	$3.75 \times 10^{-13} \text{ m}/(\text{Pa} \cdot \text{s})$	$1.34 \times 10^{-13} \text{ m}/(\text{Pa} \cdot \text{s})$
$A_{in}/V_{in}$	78 mM	78 mM	$L_s$	$3.75 \times 10^{-13} \text{ m}/(\text{Pa} \cdot \text{s})$	$8.89 \times 10^{-13} \text{ m}/(\text{Pa} \cdot \text{s})$
$C_o^{Na}$	107 mM	107 mM	$\mathcal{M}_{in}$	0.988	0.99
$C_o^K$	3 mM	3 mM	$\mathcal{M}_{ex}$	0.012	0.01
$C_m$	-	$1 \times 10^{-2} \text{ F}/\text{m}^2$	$\mathcal{M}_v$	$6 \times 10^5 / \text{m}$	$5 \times 10^5 / \text{m}$
$D_{ex}^{Na}$	-	$1.39 \times 10^{-9} \text{ m}^2/\text{s}$	$T$	-	310 K
$D_{ex}^K$	-	$2.04 \times 10^{-9} \text{ m}^2/\text{s}$	$k_e$	$1.72 \times 10^{-8} \text{ m}^2/(\text{V} \cdot \text{s})$	$1.45 \times 10^{-8} \text{ m}^2/(\text{V} \cdot \text{s})$
$D_{ex}^{Cl}$	-	$2.12 \times 10^{-9} \text{ m}^2/\text{s}$	$k_B$	$1.38 \times 10^{-23} \text{ J}/\text{K}$	$1.38 \times 10^{-23} \text{ J}/\text{K}$
$D_{in}^{Na}$	-	$1.39 \times 10^{-11} \text{ m}^2/\text{s}$	$K_{K1}$	-	1.6154 mM
$D_{in}^K$	-	$2.04 \times 10^{-11} \text{ m}^2/\text{s}$	$K_{K2}$	-	0.1657 mM
$D_{in}^{Cl}$	-	$2.12 \times 10^{-11} \text{ m}^2/\text{s}$	$K_{Na1,Na2}$	-	2.3393 mM
$e$	$1.6 \times 10^{-19} \text{ A} \cdot \text{s}$	$1.6 \times 10^{-19} \text{ A} \cdot \text{s}$	$\eta$	0.988	0.99
$g^{Na}$	$2.2 \times 10^{-3} \text{ S}/\text{m}^2$	$2.2 \times 10^{-3} \text{ S}/\text{m}^2$	$\kappa_{ex}$	$1.141 \times 10^{-16} \text{ m}^2$	$1.33 \times 10^{-16} \text{ m}^2$
$g^{Cl}$	$2.2 \times 10^{-3} \text{ S}/\text{m}^2$	$2.2 \times 10^{-3} \text{ S}/\text{m}^2$	$\kappa_{in}$	-	$9.366 \times 10^{-19} \text{ m}^2$
$G^K$	$2.1 \text{ S}/\text{m}^2$	$2.1 \text{ S}/\text{m}^2$	$\gamma_{m,s}$	1	1
$I_p$	$2.3 \times 10^{-2} \text{ A}/\text{m}^2$	-	$\tau_c$	0.16	0.16
$I_{max1}$	-	$0.478 \text{ A}/\text{m}^2$	$\mu$	$7 \times 10^{-4} \text{ Pa} \cdot \text{s}$	$7 \times 10^{-4} \text{ Pa} \cdot \text{s}$
$I_{max2}$	-	$0.065 \text{ A}/\text{m}^2$	$\bar{z}$	-1.5	-1.5

## Appendix B. Dimensionless Parameters and Scales

The following dimensionless parameters' value and scales calculation based on values in [55]

Scales/Parameters	Value	Parameters	Value
$a^{Na*}$	$6.9 \times 10^{-2} A/m^2$	$\delta_0 = \frac{\mathcal{M}_{ex}}{\mathcal{M}_{in}}$	$\frac{1}{99}$
$C^*$	$110 mM$	$\delta_1 = \frac{k_e \tau_c k_B T}{e R u_{ex}^*}$	$1.2031 \times 10^{-1}$
$O^*$	$220 mM$	$\delta_2 = \frac{\mu R u_{in}^*}{\kappa_{in} \gamma m k_B T O^*}$	$6.861 \times 10^{-3}$
$P^*$	$16.937 KPa$	$\delta_3 = \frac{P^*}{\gamma m k_B T O^*}$	$2.9894 \times 10^{-2}$
$u_{in}^*$	$3.2506 nm/s$	$\delta_4 = \frac{\mathcal{M}_{in} u_{in}^*}{R \mathcal{M}_v L m \gamma m k_B T O^*}$	$3.5323 \times 10^{-5}$
$u_{ex}^*$	$3.2181 \mu m/s$	$\delta_5 = \frac{u_{in}^*}{L_s \gamma s k_B T O^*}$	$4.3022 \times 10^{-3}$
$\phi^*$	$26.7 mV$	$\delta_6 = \frac{\mathcal{M}_v C m k_B T}{e^2 C^* \eta}$	$1.2745 \times 10^{-5}$
$D_{ex}^*$	$3.392 \times 10^{10} m^2/s$	$\delta_7 = \frac{\mathcal{M}_v C m k_B T}{e^2 C^* (1-\eta)}$	$1.2617 \times 10^{-3}$
$D_{in}^*$	$2.12 \times 10^{-11} m^2/s$	$\delta_8 = \frac{\mathcal{M}_{ex} D_{ex}^*}{\mathcal{M}_{in} D_{in}^*}$	$1.6162 \times 10^{-1}$
$Pe_{ex}$	$1.5180$	$\delta_9 = \frac{D_{in}^{Cl} - D_{in}^K}{D_{in}^*}$	$3.77 \times 10^{-2}$
$Pe_{in}$	$2.4533 \times 10^{-1}$	$\delta_{10} = \frac{D_{in}^{Cl} - D_{in}^{Na}}{D_{in}^*}$	$3.443 \times 10^{-1}$
$\tilde{D}_{in,ex}^{Na}$	$0.6557$	$\delta_{11} = \frac{C_{Cl,0}}{C_{ex,0}}$	$\frac{12.5}{110}$
$\tilde{D}_{in,ex}^K$	$0.9623$	$\rho_0$	$\frac{117}{110}$
$\tilde{D}_{in,ex}^{Cl}$	$1$	$\tilde{\mathcal{M}}_v^{in}$	$3.3859 \times 10^{-1}$
$R_s$	$4.00 \times 10^{-1}$	$\tilde{\mathcal{M}}_v^{ex}$	$2.095$

The  $\delta$  can be find in the following equations.

$$\delta_0 : \text{in eq. [13]},$$

$$\delta_1 : \text{in eq. [14a]},$$

$$\delta_2 : \text{in eq. [14b]},$$

$$\delta_3 : \text{in eq. [14b]},$$

$$\delta_4 : \text{in eq. [14c]},$$

$$\delta_5 : \text{in B.C. below eq. [14]},$$

$$\delta_6 : \text{in eq. [14e]},$$

$$\delta_7 : \text{in eq. [14f]},$$

$$\delta_8 : \text{in eq. [14h]},$$

$$\delta_9 : \text{in eq. [18]},$$

$$\delta_{10} : \text{in eq. [18]},$$

$$\delta_{11} : \text{in eq. [43]},$$

## Appendix C. Non-dimensionalization

In this section, we derive the dimensionless model based on the lens, which has been widely studied. The major ions we considering here are sodium ( $Na^+$ ), potassium ( $K^+$ ) and chloride ( $Cl^-$ ) and the sodium-potassium pump which distributed on the surface of the lens. Although we restrict ourselves in this particular problem, the following procedure can be applied in a wide range of practical problems in biological syncytia.

### Appendix C.1. Water circulation

In the following, we assume the typical length of lens is  $R$ . The fluid system is driven by the osmotic gradient, which is generated by the sodium-potassium pump on the surface. In Eq. 7, the strength of sodium-potassium pump at surface depends on the ion's concentration, which leads

$$a^{Na} = 3\frac{I_p}{e}, \quad a^K = -2\frac{I_p}{e}, \quad a^{Cl} = 0, \quad (C.1)$$

where

$$I_p = I_{max1} \left( \frac{C_{in}^{Na}}{C_{in}^{Na} + K_{Na1}} \right)^3 \left( \frac{C_o^K}{C_o^K + K_{K1}} \right)^2 + I_{max2} \left( \frac{C_{in}^{Na}}{C_{in}^{Na} + K_{Na2}} \right)^3 \left( \frac{C_o^K}{C_o^K + K_{K2}} \right)^2. \quad (C.2)$$

We assume that the velocity at surface determines the characteristic velocity scale for the problem. We have ion fluxes in the intracellular, extracellular region in Eq. 5 and trans-membrane source of ion in Eq. 6 for ion  $Na^+, K^+, Cl^-$ .

At boundary of the intracellular space, due to the ion pump in Eq. C.1 and assumption of conductance at surface that  $G^{Na} = G^{Cl} = 0$  [51, 47], we have

$$J_{in}^{Na} = a^{Na}, \quad J_{in}^K = j_s^K + a^K, \quad J_{in}^{Cl} = 0. \quad (C.3)$$

Since  $g^K = 0$  inside of the lens, we obtain

$$j_s^K + a^K = 0. \quad (C.4)$$

This assumption obviously will have to be replaced in applications to other tissues, with a less particular distribution of channel proteins.

By the conservation of fluxes for each ion in Eq. 4, we get

$$J_{in}^i = -\delta_0 J_{ex}^i, \quad i = Na, K, Cl, \quad (C.5)$$



where  $\delta_0 = \frac{M_{ex}}{M_{in}}$ . Therefore, Eq. C.3 becomes

$$-\delta_0 J_{ex}^{Na} = a^{Na}, \quad -\delta_0 J_{ex}^K = 0, \quad -\delta_0 J_{ex}^{Cl} = 0. \quad (C.6)$$

Adding up all three fluxes in Eq. C.6 and since in the extracellular region each ion diffusion coefficient are at the same level of approximation, i.e.

$$D_{ex}^i = O(D_{ex}), \quad i = Na, K, Cl, \quad (C.7)$$

and based on Eq. 10, we get

$$O_{ex} u_{in} + \delta_0 D_{ex} \tau_c \frac{d}{dr} O_{ex} + \frac{D_{ex} \tau_c \delta_0}{k_B T} \rho_{ex} \frac{d}{dr} \phi_{ex} = a^{Na}. \quad (C.8)$$

The strength of the ion pump  $a^{Na}$  depends on the ion concentration in Eq. C.2. We choose the scale of  $a^{Na}$  is  $a^{Na*}$  based on an experimental estimation [51]. Using Eq. C.8, we take the scale for  $O_{in,ex}$  and  $u_{in}$  to be  $O^*$  and  $u_{in}^*$  as

$$O^* = 2 \left( C_o^{Na} + C_o^K \right), \quad u_{in}^* = \frac{a^{Na*}}{O^*}. \quad (C.9)$$

By mass conservation expressed in Eq. 1, we naturally get the scale of  $u_{ex}$  as

$$u_{ex}^* = \delta_0^{-1} u_{in}^*. \quad (C.10)$$

Furthermore,  $\phi^* = \frac{k_B T}{e}$  is used for the scale of electric potential  $\phi_{in}$  and  $\phi_{ex}$ . For the extracellular velocity in Eq. 2, we have

$$u_{ex}^* \tilde{u}_{ex} = -\frac{\kappa_{ex}}{\mu R} \tau_c P_{ex}^* \frac{d}{dr} \tilde{P}_{ex} - k_e \tau_c \frac{k_B T}{e R} \frac{d}{dr} \tilde{\phi}_{ex}, \quad (C.11)$$

We think the  $\frac{d}{dr} P_{ex}$  term balance the velocity  $u_{ex}$ . The scale for extracellular pressure  $P_{ex}^*$  is then choose

$$P_{ex}^* = \frac{\mu R u_{ex}^*}{\kappa_{ex} \tau_c}.$$

Therefore, we get

$$\tilde{u}_{ex} = -\frac{d}{dr} \tilde{P}_{ex} - \delta_1 \frac{d}{dr} \tilde{\phi}_{ex}, \quad (C.12)$$

where  $\delta_1 = \frac{k_e \tau_c k_B T}{e R u_{ex}^*}$ . For the intracellular velocity, we have

$$u_{in}^* \tilde{u}_{in} = -\frac{\kappa_{in} P_{in}^*}{\mu R} \frac{d}{d\tilde{r}} \tilde{P}_{in} + \frac{\kappa_{in} \gamma_m k_B T O^*}{\mu R} \frac{d}{d\tilde{r}} \tilde{O}_{in}. \quad (C.13)$$

We claim term  $\frac{d}{d\tilde{r}} \tilde{P}_{in}$  and  $\frac{d}{d\tilde{r}} \tilde{O}_{in}$  balance at the same level. Therefore, we choose the same scale for the intracellular and extracellular pressure, namely,

$$P^* = P_{in}^* = P_{ex}^*.$$

Then Eq. C.13 becomes

$$\delta_2 \tilde{u}_{in} = -\delta_3 \frac{d}{d\tilde{r}} \tilde{P}_{in} + \frac{d}{d\tilde{r}} \tilde{O}_{in}, \quad (C.14)$$

where

$$\delta_2 = \frac{\mu R u_{in}^*}{\kappa_{in} \gamma_m k_B T O^*}, \quad \delta_3 = \frac{P^*}{\gamma_m k_B T O^*}.$$

In all, the fluid system Eq. 1 becomes

$$\begin{cases} \tilde{u}_{ex} = -\tilde{u}_{in}, \\ \delta_4 \frac{1}{\tilde{r}^2} \frac{d}{d\tilde{r}} (\tilde{r}^2 \tilde{u}_{in}) = \delta_3 (\tilde{P}_{ex} - \tilde{P}_{in}) + (\tilde{O}_{in} - \tilde{O}_{ex}), \end{cases} \quad (C.15)$$

with boundary condition

$$\begin{cases} \tilde{P}_{ex} = 0, \\ \delta_5 \tilde{u}_{in} = \delta_3 \tilde{P}_{in} - (\tilde{O}_{in} - \tilde{O}_{ex}), \end{cases}$$

where

$$\delta_4 = \frac{\mathcal{M}_{in} u_{in}^*}{R \mathcal{M}_v L_m \gamma_m k_B T O^*}, \quad \delta_5 = \frac{u_{in}^*}{L_s \gamma_s k_B T O^*}.$$

## Appendix C.2. Ions circulation

The velocity scales and diffusion coefficients in the extracellular and intracellular space are at different levels of approximation in our approach. In the following, we put the characteristic diffusion coefficients at intracellular and extracellular region and scale of concentration as

$$D_{ex}^* = D_{ex}^{Cl} \tau_c, \quad D_{in}^* = D_{in}^{Cl}, \quad C^* = C_o^{Na} + C_o^K.$$

In this way, we get Peclet number in the extracellular and intracellular and dimensionless Nernst potential as

$$Pe_{in} = \frac{u_{in}^* R}{D_{in}^*}, \quad Pe_{ex} = \frac{u_{ex}^* R}{D_{ex}^*}, \quad \tilde{E}^i = \frac{1}{z^i} \log \left( \frac{\tilde{C}_{ex}^i}{\tilde{C}_{in}^i} \right).$$

Because  $g^{Na} = 0$  inside of lens, we have  $K^+$  system as in Mathias's model [51],

$$\begin{cases} \frac{1}{\tilde{r}^2} \frac{d}{d\tilde{r}} \left( \tilde{r}^2 \left( Pe_{ex} \tilde{C}_{ex}^K \tilde{u}_{ex} - \tilde{D}_{ex}^K \left( \frac{d}{d\tilde{r}} \tilde{C}_{ex}^K + z^K \tilde{C}_{ex}^K \frac{d}{d\tilde{r}} \tilde{\phi}_{ex} \right) \right) \right) = 0, \\ \frac{1}{\tilde{r}^2} \frac{d}{d\tilde{r}} \left( \tilde{r}^2 \left( Pe_{in} \tilde{C}_{in}^K \tilde{u}_{in} - \tilde{D}_{in}^K \left( \frac{d}{d\tilde{r}} \tilde{C}_{in}^K + z^K \tilde{C}_{in}^K \frac{d}{d\tilde{r}} \tilde{\phi}_{in} \right) \right) \right) = 0, \end{cases} \quad (C.16)$$

with boundary condition

$$\begin{cases} \tilde{C}_{ex}^K = \tilde{C}_o^K, \\ Pe_{in} \tilde{C}_{in}^K \tilde{u}_{in} - \tilde{D}_{in}^K \left( \frac{d}{d\tilde{r}} \tilde{C}_{in}^K + z^K \tilde{C}_{in}^K \frac{d}{d\tilde{r}} \tilde{\phi}_{in} \right) = \frac{R_s}{z^K} (\tilde{\phi}_{in} - \tilde{E}^K) + \tilde{a}^K, \end{cases}$$

and  $Cl^-$  system as

$$\begin{cases} \frac{1}{\tilde{r}^2} \frac{d}{d\tilde{r}} \left( \tilde{r}^2 \left( Pe_{ex} \tilde{C}_{ex}^{Cl} \tilde{u}_{ex} - \tilde{D}_{ex}^{Cl} \left( \frac{d}{d\tilde{r}} \tilde{C}_{ex}^{Cl} + z^{Cl} \tilde{C}_{ex}^{Cl} \frac{d}{d\tilde{r}} \tilde{\phi}_{ex} \right) \right) \right) = \frac{\tilde{\mathcal{M}}_v^{ex}}{z^{Cl}} (\tilde{\phi}_{in} - \tilde{\phi}_{ex} - \tilde{E}^{Cl}), \\ \frac{1}{\tilde{r}^2} \frac{d}{d\tilde{r}} \left( \tilde{r}^2 \left( Pe_{in} \tilde{C}_{in}^{Cl} \tilde{u}_{in} - \tilde{D}_{in}^{Cl} \left( \frac{d}{d\tilde{r}} \tilde{C}_{in}^{Cl} + z^{Cl} \tilde{C}_{in}^{Cl} \frac{d}{d\tilde{r}} \tilde{\phi}_{in} \right) \right) \right) \\ = -\delta_8 \frac{1}{\tilde{r}^2} \frac{d}{d\tilde{r}} \left( \tilde{r}^2 \left( Pe_{ex} \tilde{C}_{ex}^{Cl} \tilde{u}_{ex} - \tilde{D}_{ex}^{Cl} \left( \frac{d}{d\tilde{r}} \tilde{C}_{ex}^{Cl} + z^{Cl} \tilde{C}_{ex}^{Cl} \frac{d}{d\tilde{r}} \tilde{\phi}_{ex} \right) \right) \right), \end{cases} \quad (C.17)$$

with boundary condition

$$\begin{cases} \tilde{C}_{ex}^{Cl} = \tilde{C}_o^{Na} + \tilde{C}_o^K + \delta_7 (\tilde{\phi}_{in} - \tilde{\phi}_{ex}), \\ Pe_{in} \tilde{C}_{in}^{Cl} \tilde{u}_{in} - \tilde{D}_{in}^{Cl} \left( \frac{d}{d\tilde{r}} \tilde{C}_{in}^{Cl} + z^{Cl} \tilde{C}_{in}^{Cl} \frac{d}{d\tilde{r}} \tilde{\phi}_{in} \right) = 0. \end{cases}$$

where

$$R_s = \frac{G^K k_B T R}{e^2 D_{in}^* C^*}, \quad \tilde{a}^K = \frac{a^K R}{D_{in}^* C^*}, \quad \tilde{\mathcal{M}}_v^{ex} = \frac{\mathcal{M}_v g^{Cl} k_B T R^2}{\mathcal{M}_{ex} e^2 D_{ex}^* C^*}, \quad \delta_8 = \frac{\mathcal{M}_{ex} D_{ex}^*}{\mathcal{M}_{in} D_{in}^*}.$$

The concentration of  $Na^+$  can be solved from the following equations

$$\begin{cases} \sum_i z^i \tilde{C}_{in}^i + \tilde{z} \frac{\tilde{A}_{in}}{V_{in}} = \delta_6 (\tilde{\phi}_{in} - \tilde{\phi}_{ex}), \\ \sum_i z^i \tilde{C}_{ex}^i = -\delta_7 (\tilde{\phi}_{in} - \tilde{\phi}_{ex}), \end{cases} \quad (C.18)$$

where

$$\delta_6 = \frac{\mathcal{M}_v C_m k_B T}{e^2 C^* \eta}, \quad \delta_7 = \frac{\mathcal{M}_v C_m k_B T}{e^2 C^* (1 - \eta)}. \quad (\text{C.19})$$

From Eq. 11 and use the fact  $z^{Na} = z^K = 1$  and assumption that  $g^{Na} = g^{Cl}$  and  $G^{Na} = G^{Cl} = 0$ , we have

$$\begin{cases} \frac{1}{\tilde{r}^2} \frac{d}{d\tilde{r}} \left( \tilde{r}^2 \left( Pe_{ex} \tilde{\rho}_{ex} \tilde{u}_{ex} - \sum_i \tilde{D}_{ex}^i z^i \frac{d}{d\tilde{r}} \tilde{C}_{ex}^i - \tilde{\sigma}_{ex} \frac{d}{d\tilde{r}} \tilde{\phi}_{ex} \right) \right) = \tilde{\mathcal{M}}_v^{ex} \left( 2 (\tilde{\phi}_{in} - \tilde{\phi}_{ex}) - \tilde{E}^{Na} - \tilde{E}^{Cl} \right), \\ \frac{1}{\tilde{r}^2} \frac{d}{d\tilde{r}} \left( \tilde{r}^2 \left( Pe_{in} \tilde{\rho}_{in} \tilde{u}_{in} - \sum_i \tilde{D}_{in}^i z^i \frac{d}{d\tilde{r}} \tilde{C}_{in}^i - \tilde{\sigma}_{in} \frac{d}{d\tilde{r}} \tilde{\phi}_{in} \right) \right) \\ = -\delta_8 \frac{1}{\tilde{r}^2} \frac{d}{d\tilde{r}} \left( \tilde{r}^2 \left( Pe_{ex} \tilde{\rho}_{ex} \tilde{u}_{ex} - \sum_i \tilde{D}_{ex}^i z^i \frac{d}{d\tilde{r}} \tilde{C}_{ex}^i - \tilde{\sigma}_{ex} \frac{d}{d\tilde{r}} \tilde{\phi}_{ex} \right) \right), \end{cases} \quad (\text{C.20})$$

with boundary condition

$$\begin{cases} \tilde{\phi}_{ex} = 0, \\ Pe_{in} \tilde{\rho}_{in} \tilde{u}_{in} - \sum_i \tilde{D}_{in}^i z^i \frac{d}{d\tilde{r}} \tilde{C}_{in}^i - \tilde{\sigma}_{in} \frac{d}{d\tilde{r}} \tilde{\phi}_{in} = \frac{R_s}{z^K} (\tilde{\phi}_{in} - \tilde{E}^K) + \tilde{I}_p^\phi, \end{cases} \quad (\text{C.21})$$

where

$$\tilde{\rho}_{in} = |\tilde{z}| \frac{\widetilde{A_{in}}}{V_{in}} + \delta_6 (\tilde{\phi}_{in} - \tilde{\phi}_{ex}), \quad \tilde{\rho}_{ex} = \delta_7 (\tilde{\phi}_{ex} - \tilde{\phi}_{in}), \quad \tilde{I}_p^\phi = \frac{I_p R}{e D_{in}^* C^*},$$

and

$$\tilde{\sigma}_{in} = \sum_i \tilde{D}_{in}^i (z^i)^2 \tilde{C}_{in}^i, \quad \tilde{\sigma}_{ex} = \sum_i \tilde{D}_{ex}^i (z^i)^2 \tilde{C}_{ex}^i.$$

## Appendix D. Effect of permeability

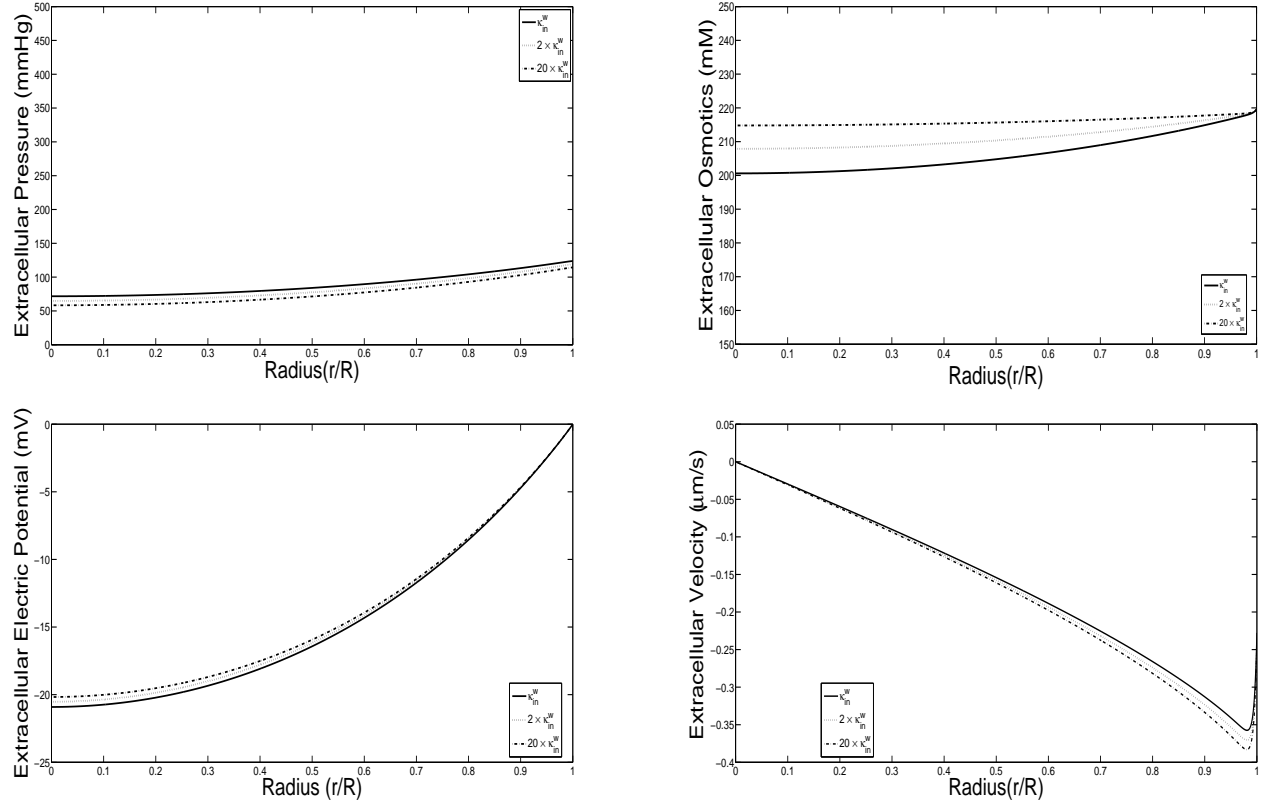


Figure D.5: Comparison between different  $\kappa_{in}$ .